

Appl. № 10/708,191
Amdt. dated 6 April 2006
Reply to Office Action of 28 December 2005

Confirmation №. 2190
Attorney Docket № ARL 04-01

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Amendments to the Specification:

Please replace paragraph [0046] with the following amended paragraph:

[0046] Referring to FIG. 1A-FIG. 1C & FIG. 2 an aerosol particle analyzer (APA) 100 is immersed in a gas such as the atmosphere, having particles therein. Generally, the particles include many types of particles 124, some of which may contain no analyte 80, and some of which may contain some amount of the analyte 80. The particles 124 may be liquid, solid, or a mixture of liquid and solid.

Please replace paragraph [0048] with the following amended paragraph:

[0048] The measurement of the analyte 80 in the particles 124 is accomplished as follows. The pump draws gas 120 and particles 124 into the APA 100 through an induction port 126 then through a charger 250 that imparts a negative charge to the particles 124, then through the particle-droplet-collision subsystem (PDCS) 400, and then exhausts at least the gas 120 out of an eduction port. The charged-droplet generator (CDG) 200 ejects a charged-droplet-of-the-analysis-liquid CDAL 150 into the flow of gas 120 and particles 124 being drawn into the (PDCS) 400, with a direction and velocity such that it enters PDCS 400 substantially along the PDCS axis 402 and then is levitated. A Y-connector tube 148 connects the charger 250 to the PDCS 400 and also connects the CDG 200 to the PDCS 400 in a way that allows the CDAL 150 ejected from the CDG 200 to enter the PDCS 400 along the PDCS axis 402. As the particles flow through the PDCS 400, at least some of the particles 124 collide with the CDAL 150 and combine with it. The polarity of the charge imparted to the particles 124 by the charger 250 is the opposite of the polarity of the CDAL 150, so that electrostatic forces increase the number of the particles 124 that combine with the CDAL 150. More than one particle 124 may combine with the CDAL 150. The charge on the CDAL 150 remains substantially the same as that of the CDAL 150 ejected from the CDG 200 because the magnitude of the charge on the particles 124 that combine with the CDAL 150 is substantially smaller than the charge of the CDAL 150. If one or more of the particle(s) 124 that mix with to CDAL 150 contain some analyte 80, the fluorescence of the

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CDAL 150 begins to change in accordance with the amount of the analyte 80. After a time, the CDAL 150 is ejected by the PDCS 400, and moves into the droplet analysis system DAS 600. In the DAS 600 the CDAL 150 is levitated for time sufficient for the analyte 80 to react with the analysis liquid to generate fluorescence, and then the fluorescence of the CDAL 150 is measured. The amount of the analyte 80 in the particles that collided with the CDAL 150 is determined from this measured fluorescence. When the CDAL 150 is ejected, the CDG 200 injects another CDAL 150 into the PDCS 400. A computer, controller, voltage sources and electronics subsystem (CCVSES) controls the timing of the generation of the CDAL 150, the motion of the CDAL 150, and the measurement of the fluorescence and the determination of the amount of analyte from that measured fluorescence.

Please replace the paragraph [0049] with the following amended paragraph:

[0049] By using only a small amount of the analysis liquid 800, i.e., the amount of analysis liquid 800 in a CDAL 150, for each measurement, the APA 100 satisfies one objective of the APA 100. By keeping the CDAL 150 levitated from the time of generation of the CDAL 150 to the time of measurement of the fluorescence, the APA 100 avoids contact of the CDAL 150 with any surface, and thereby eliminates cross contamination and reduces the need for replacing expendable items, thereby satisfying another objective of the APA 100. By separating the PDCS 400, in which the gas 120 flowing past the CDAL 150 may have a very low humidity, from the DAS 600, which is airtight except for the inlet orifice 632 through which CDAL 150 from the PDCS 400 enters, and so the humidity in the DAS 600 can be kept high enough that the CDAL 150 evaporates slowly enough, that the reaction between the analyte 80 and the analysis liquid 800 has time to take place, and so the amount of analyte ~~[[800]]~~ 80 can be determined.

Please replace the paragraph [0054] with the following amended paragraph:

[0054] FIG. 2 illustrates schematically one embodiment of the reaction that takes place in the CDAL 150 when analyte 80 is present in the particle 124 that combined with the CDAL 150. FIG. 2 shows how the fluorescence of the analysis liquid 800 changes, so that the fluorescence of the CDAL 150 varies with the amount of analyte 80 in the particles 124 that

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combined with the CDAL 150. The example shown in FIG. 2 is a variation of that shown in Figure 6A of an article by R. L. Nutiu and Y. F. Li, "Structure-switching signaling aptamers," Journal of the American Chemical Society, 125, 4771-4778 (2003), (herein incorporated by reference, especially their Figure 6A. In FIG. 2, the structure-switching signaling aptamer 820 is comprised of: (i) an aptamer (MAP) 822 chosen because it binds selectively to the analyte 80, (ii) a DNA oligonucleotide, Stem-2 824, which is covalently linked to the MAP 822; (iii) a DNA oligonucleotide, Stem-1 826 that is covalently linked to Stem-2 824; (iv) a fluorophore (F) 828; (v) DNA oligonucleotide (FDNA) 830 that is linked to the fluorophore 828; (vi) a quencher (Q) 832; and (vii) a DNA oligonucleotide (QDNA) 834 that is linked to the quencher 832. The FDNA 830 forms the DNA duplex with Stem-2 822. The QDNA 834 forms the DNA duplex with Stem-1. In this structure-switching signaling aptamer 820, the fluorophore 828 and the quencher 832 are held near each other and the quencher 832 quenches the fluorescence of the fluorophore 828, so that the fluorophore 828, fluoresces very weakly if at all. When the analyte 80 is present, the MAP 822 of the structure switching signaling aptamer 820 binds to the analyte 80 as illustrated in FIG. 2, and thereby releases the FDNA 830 so that the fluorophore 828 is no longer quenched, and can fluoresce brightly. The reaction illustrated in FIG. 2 differs from that shown in Fig. 6A of Nutlu and Li, in that the F 828 and Q 832 are interchanged so that the FDNA 830 diffuses relatively rapidly, even in cases where the analyte 80 has a high molecular weight. The FDNA 830 can diffuse throughout the CDAL 150 even if the analyte 80 is bound to the surface of the particle 124 and the particle 124 is too large to diffuse significantly. This ability of the fluorophore 828 to diffuse relatively rapidly throughout the CDAL 150 is important because otherwise it can be much more difficult to measure the amount of the fluorophore (F) that is unquenched in the CDAL 150 (see e.g., S. C. Hill et al., "Simulation of single-molecule photocount statistics in microdroplets," Analytical Chemistry, 70, 2964-2971 (1998)). For cases where the analyte 80 is an oligonucleotide, the approach illustrated in FIG. 2 is used in one exemplar, but for these analytes 80 the aptamer (MAP) 822 is an oligonucleotide that is complementary to the analyte 80.

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Please replace the paragraph [0058] with the following amended paragraph:

[0058] FIG. 3E illustrates another exemplar of the PDCS 400 that is suitable for use with the APA 100 shown in FIG. 1B. In addition to most of the components illustrated in FIG. 3A, this PDCS 400 includes a cubic EDB (CEDB) ~~[[460]]~~ 464 of the type described by E. E. Allison and B. R. F. Kendall, "Cubic electrodynamic levitation trap with transparent electrodes," *Reviews of Scientific Instruments*, 67, 3806-3812 (1996), especially Figs. 1 and 2, p. 3807, and the CEDB used by R. A. Shaw, D. Lamb, and A. M. Moyle, "An Electrodynamic Levitation System for Studying Individual Cloud Particles under Upper-Tropospheric Conditions," *Journal of Atmospheric and Oceanic Technology*, 17, 940-948 (2000), both herein incorporated by reference. In FIG. 3E, the CEDB is aligned so that only one of the six CEDB electrodes 464 is visible. In the work of Kendall et al., and Shaw et al., referenced above, the electrode can take up the whole side of the cube, with only small spacer regions between these electrodes, and small holes can be cut in these electrodes without causing droplets to be levitated substantially less well. In the exemplar illustrated in FIG. 3E, the CDAL 150 is levitated in the CEDB 460 while the gas 120 and particles 124 flow past it so that the CDAL 150 and particles 124 can collide. In FIG. 3E, the CDAL 150 enters through orifice 448D, and the gas 120 and particles 124 enter through 448E. To levitate the CDAL 150 for collisions with the particles 124, the voltages on the OEDB 460 are as described by Shaw et al. (2000) referenced above, that is, alternating current (AC) voltages are applied to those electrodes 464 that are parallel to the vertical direction, shown with a z-axis 406, while only direct current (DC) voltages are applied to the electrodes perpendicular to the z axis 406. Once it is time to eject the CDAL 150, the voltages applied to the CEDB are switched so that the AC voltages are applied to the four electrodes that are parallel to the z axis 406, and DC voltages are applied to the electrodes perpendicular to the z axis so that the CDAL 150 is pushed toward, and then into the LQ-PDCS 410. Then the CDAL 150 is ejected from the LQ-PDCS 410 into the DAS 600 as described above. Levitation of the CDAL 150 while the flow of the gas 120 is upward requires a smaller DC voltage to counter the gravitational force on the CDAL 150, and so the voltages applied to the electrodes 464 are smaller, and so the DC

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fields that push both the CDAL 150 and the particles 124 are smaller. Also in FIG. 3E is a laser diode 490 to illuminate the CDAL 150 and a video camera 492 to monitor the position of the CDAL 150 so that the voltages applied to the electrodes ~~[[460]]~~ 464 can be adjusted to stabilize the particle position as described by D. Lamb, A. M. Moyle, and W. H. Brune, "The Environmental Control of Individual Aqueous Particles in a Cubic Electrodynamic Levitation System," Aerosol Science and Technology, 24, 263-278 (1996), especially p. 265, herein incorporated by reference. ~~[FIG. 3F illustrates a]~~ Another exemplar of the PDCS 400 that is suitable for use with the APA 100 shown in FIG. 1C. It does not include the plate 440 of the PDCS shown in FIG. 3E.

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Please replace the paragraph [0064] with the following amended paragraph:

[0064] Another exemplar of the APA 100 is shown in FIG. 5. A vertically oriented linear quadrupole (LQ) 910 is surrounded by an airtight container 920 that is connected below to the charger 250 and CDG 200, and is connected above to a tube 924 that is connected to an impactor 930 which is connected with a pipe 446 to a pump 190. Impactors are discussed, for example, in W. C. Hinds, Aerosol Science and Technology: Properties Behavior and Measurement of Airborne Particles (Wiley, New York, 1982), especially pp. 113-124, included herein by reference. The pump 190 lowers the pressure in the tube and the top of the LQ 910 so that the CDAL 150 and particles 124 are drawn upward through the LQ 910 and are focused substantially near the axis of the LQ 910 so that the particles and CDAL 150 tend to combine with each other as they travel upward through the LQ 910 so that the fluorescence of the CDAL 150 can change according to the amount of the analyte 80 in the particles 124. A laser diode 990, a filter 992, a photodetector 994 and lenses 996 are used to measure the fluorescence of the CDAL as it exits the LQ 910 so that the amount of analyte in the particles can be determined. Because this exemplar shown in FIG. 5 has no DAS 600, this exemplar is applicable to combinations of particles 124, analytes 80, and analysis liquids 800 for which the reactions between the particle 24 and the CDAL 150 occur relatively quickly, for example in a case where the analyte 80 is known to occur in particles 124 that are liquid, or in cases where the analyte 124 occurs in a high concentration in the particles 124, and the analyte 80 dissolves especially quickly in the analysis liquid 800, and the required accuracy for the measurement of the amount of analyte 80 is not too high.

Please replace the paragraph [0065] with the following amended paragraph:

[0065] Another exemplar of the APA 100 is shown in FIG. 6. The CDAL 150 is injected from the CDG ~~[[250]]~~ 200 into a particle-droplet-collision-and-analysis subsystem (PDCAS) 950 where it is levitated by a CEDB 460 and combines with particles 124 that are have been drawn through the charger 250. A laser diode 990, a filter 992, a photodetector 994, and lenses 996 are used to measure the fluorescence of the CDAL 150 as the CDAL 150 is levitated in the PDCAS 950. The APA 100 in FIG. 6 is similar to that illustrated in FIGS. 1B

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and 1C, with the major difference being that there is no DAS 600 to keep the humidity high in order to reduce the evaporation rate of the CDAL 150. Because there is no DAS 600 in the exemplar shown in FIG. 6, this exemplar is applicable to combinations of particles 124, analytes 80, and analysis liquids 800 for which the reactions between the particle 24 and the CDAL 150 occur relatively quickly, for example in a case where the analyte 80 is known to occur in particles 124 that are liquid, or in cases where the analyte 124 occurs in a high concentration in the particles 124, and the analyte 80 dissolves especially quickly in the analysis liquid 800, and the required accuracy for the measurement of the amount of analyte 80 is not too high.

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